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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,270	GRIFFITHS, LYNETTE ROBYN	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,15 and 17-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3, 4, 15, 17-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed February 28, 2006 is acknowledged and has been entered. Claims 1 and 4 have been amended. Claims 2, 5-14 and 16 have been canceled. Claims 17-29 have been added. Claims 1, 3, 4, 15 and 17-29 are pending. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous rejections

3. The claim rejection under 35 USC 112 first paragraph for lacking enablement is withdrawn for claims 2, 5-14 and 16 in view of cancellation of those claims by Applicant. This rejection is however maintained for claims 1, 3, 4, and 15 and is discussed below along with the newly added claims 17-29 under the section "New Grounds of Rejection". The claim rejection under 35 USC 112 second paragraph is withdrawn in view of Applicant's amendments. The prior art rejection under 35 USC 102 directed to claims 1, 3, 5, 6, 12 and 14 as being anticipated by Xu et al is withdrawn in view of Applicant's amendment. The prior art rejection under 35 USC 102 directed to claims 1-2, 5 and 12-13 as being anticipated by Bellamy et al is withdrawn in view of Applicant's amendment.

New Ground(s) of Rejections

THE NEW GROUNDS OF REJECTIONS WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

Claim Rejections - 35 USC § 112: Lack of Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3, 4, 15 and newly added claims 17-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is "undue". These factors include but are not limited to: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented in the specification, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the unpredictability of the art and (8) the breadth of the claims. (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)) *(MPEP 2164.01(a))*.

Enablement Issues

This enablement rejection is based on several fundamental enablement problems with the claims noted above. The first problem with the claims 1, 3, 4, 15 and 17-29 is that theses claims are drawn to a method for diagnosing and/or treatment of hypertension or a predisposition to hypertension which has a final process step which comprises "determining a risk polymorphism in the promoter of an inducible nitric oxide synthase (iNOS) gene, wherein the risk

polymorphism is a four base pair insertion located between the position -891 and 576- to the transcription start site in the promoter of the iNOS gene, whereby diagnosis of hypertension or a predisposition thereto is determined based upon the presence or absence of the risk polymorphism. The specification does not, however, teach sufficient use for this determination. A diagnosis has a use; it is simply that there is no enablement for the diagnosis given the identification of any polymorphism or risk polymorphism in the iNOS gene at the position identified.

The nature of the invention

The claims are drawn to a method for diagnosing hypertension or a predisposition to hypertension by determining whether a risk polymorphism is present in the promoter of an inducible iNOS gene, wherein the risk polymorphism is a four base pair insertion located between the position -891 and 576- to the transcription start site in the promoter of the iNOS gene, whereby diagnosis of hypertension or a predisposition thereto is determined based upon the presence or absence of the risk polymorphism.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology". *Mycogen Plant Sci*, Inc, v, *Monsanto Co.* 243, F3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are dawn to any polymorphism comprising a four base pair insertion between positions -891 and -575 in the promoter of an iNOS gene. Thus the claims can encompass any polymorphism, including silent polymorphism in the promoter of an iNOS gene whether it be associated with a disease or condition, such as hypertension or not. Arguably, every

polymorphism that may be found in a gene is not always associated with a disease or condition. Further, any polymorphism(s) within the region identified that may be present in the iNOS gene may not necessarily be associated with hypertension. In fact, the art teaches the identification of risk polymorphism in the promoter of the iNOS gene that is associated with other diseases, such as atopy (see Konno et al, J. Allergy Clin. Immunol, Vol. 108, pages 810-814) and asymptomatic malaria-endemic populations (see Boutlis et al., Am. J. Trop Hyg. Vol. 60, No. 6, pages 569-573, 2003). The associations of theses risk polymorphisms in the promoter of the iNOS gene are associated with diseases with radically different etiologies, symptoms and with no relationship to each other or to hypertension. The claims as broadly written encompass any possible mutation or polymorphism located between the position -891 and 576- to the transcription start site in the promoter of the iNOS gene and speculates that this polymorphisms is associated with a risk of hypertension. The specification fails to define the sequence of the four base pair insertion that is claimed to be associated with hypertension. Thus the claims encompass any four base pair insertion (4^4 sequences) located anywhere between positions -891 and -571 5' to the transcription start site in the promoter of the iNOS gene and any disease that may be associate therewith. Hence, the specification is not fully commensurate in scope with the claims.

Quantity of Experimentation

The quantity of experimentation in this area is immense since there are numerous mutations and/or polymorphism that may be found in the promoter area of the iNOS gene that may be associated with a variety of different diseases. It would require significant study and experimentation including dozens of patients to determine that every possible four base pair insertion between position -891 and 576- to the transcription start site of the promoter of the

iNOS gene is associated with a risk of a disease or hypertension. This would be an inventive, unpredictable and difficult undertaking in itself, and efficacy of any of the plethora of polymorphisms as diagnostic for any particular disease, need to be demonstrated in a variety of patients with a statistically significant result. This would require year of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Wacholder et al (J. Natl. Cancer Institute (2004), Vol. 96, no. 6, pages 434-442) notes with regards to association of mutations studies that larger studies with 1500 participates have significantly more statistical power than smaller studies (see page 435). So the quantity of experimentation factor supports the conclusion that a large quantity of experimentation, with the use of may hundreds, perhaps even thousands, of patient samples would be necessary to demonstrate an association of a four base pair risk polymorphism between the position -891 and 576- to the transcription start site in the promoter of an iNOS gene. To cover any fraction of the range of diseases that may be related to a polymorphism in that promoter region of the iNOS gene would involve tens of thousands of separate patients and the associated analyses would be required. Thus undue experimentation is left to one of skill in the art to practice the invention as claimed.

Working Examples and Guidance in the specification

The specification has no working examples of any of the many diseases which are associated either generically with a polymorphism or mutation in the promoter region of the iNOS gene or with any particular polymorphism or mutation sequence. While the specification has identified by name; not sequence, a four base pair insertion located between position -891

and -575 to the transcription start site in the promoter of the iNOS gene to be associated with hypertension, the specification provides no association of *any* four base pair insertion in that region in the promoter region being associated with hypertension or any other diseases or condition. No correlation is made between any four base insertion of the promoter being associated with a risk or predisposition to hypertension. The specification provides no guidance on the plethora of possible risk and non-risk polymorphism encompassed by the claims. The specification only provides some guidance on a single four base pair insertion that is claimed to be associated with hypertension, but provides no sequence for the four base pair insertion or provide any limiting factor as to which of the numerous four base pair insertions, which are encompassed by the claims, are effective as indicating a risk to hypertension. The specification provides no guidance on methods or techniques to demonstrate what the sequence of the four base pair insertion is that is claimed to be associated with hypertension. Due to the lack of working examples and guidance in the specification, undue experimentation is left to one of skill in the art to obtain the invention as claimed.

Unpredictability in the Art

The art teaches that it is unpredictable how a polymorphism in the promoter region of the iNOS gene is associated with any particular disease (see Boltlis et al., which teaches a polymorphism in the promoter region of the iNOS gene being associated with Malaria and Konno et al., which teaches wherein a polymorphism in the promoter region of the iNOS gene is associated with atopy). Moreso, it is unpredictable that every risk polymorphism (every four base pair insertion between positions -891 and -575 5' the transcription site in the promoter) found in the promoter of the iNOS gene will be associated with hypertension. The absence of a specific relationship between a particular polymorphism

(sequence) and hypertension is the central unpredictable element.

Thus, giving the unpredictability in the art, the lack of guidance and absence of working examples in the specification, the complex nature of the invention and the breadth of the claims which fails to recite more specifically which polymorphisms are specifically associated with which disease, the experimentation left to one of skill in the art is extensive and undue.

Applicant's Traversal

6. Applicant traverses the rejection on the following ground: Applicant summarizes the Examiner's rejection. Applicant states that the Examples section of the specification describes a study demonstrating that a four base-pair insertion located in the region defined by the claim is associated significantly with hypertension. A p-value of 0.016 showed there was a statistically significant association of the four base pair insertion with risk of hypertension in a significant number of hypertensive and normotensive subjects. Applicant asserts that this section of the specification teaches subject selection criteria, methodology for obtaining nucleic acid samples from subjects, methodology for amplifying and analyzing genotypes of the isolated nucleic acids, and methods for determining whether there is an association between a particular polymorphism and hypertension. Applicant states that the specification provides working examples for determining the presence or absence of a hypertension-associated four base pair insertion in the region specified by the claims. Applicant states that the working example therefore provides clear guidance to a person of ordinary skill in the art for carrying out the method for diagnosing hypertension or predisposition thereto. Applicant states that any other four base pair insertion in the region specified by the claims can be identified by a person of ordinary skill in the art by routine experimentation. Applicant asserts that given the 316 base pairs in the claimed region

is defined and relatively small, the person of ordinary skill in the art could identify any four base pair insertion by routinely conducting known genotyping procedures in additional hypertensive and normotensive subjects. Applicant states that any nucleic acid with a different size or molecular weight than detected in the specification, for example could be sequenced to determine whether the modification is a four base pair insert. Applicant contends that with the specification's guidance that the region defined by the claims is associated with hypertension, the person of ordinary skill in the art could conduct a refined search of additional four base pair insertion by routine experimentation. Applicant states that the experimentation would be routine especially in view of the high level of skill in the art in the genomic fields. Applicant contends that because the specification provides working examples and specific guidance for conducting the claimed methods and because any experimentation for carrying out the full scope of the claimed method is no undue, the claimed methods are in accord with the enablement requirements articulate in *In re Wands* and *Ex Parte Foreman*.

Applicant states that in view of these features of the claimed method and the teachings in the specification, the Applicant do not understand certain statements in the office action. Applicant states that for example, the office states that "the claims can encompass any genotype, disease associated with or not that can be found in the iNOS gene". Applicant states that this statement is not understood as the claimed methods are directed to diagnosing hypertension or a predisposition thereto by determining whether a risk polymorphism is preset. Applicant states that thus the claims are directed to detecting the presence or absence of a polymorphism associated with hypertension because it is a "risk" polymorphism. Applicant states that the Office states that the specification identifies a four base pair insertion that may be associated

with hypertension and cites Wacholder et al for the assertion that studies with thousands of participants have more statistical power than studies with a smaller number of participants. Applicant states that these positions are not understood. Applicant states that these studies in the specification were conducted with a statistically significant number of subjects and risk of hypertension was determined with statistical significance (not p-value). Applicant states that while larger groups of subjects may provide additional statistical power in such studies, group of the size studied in the specification can provide statistically significant disease associations and thereby support the claimed method. Finally, Applicant request the rejection be withdrawn.

Examiner's Response

7. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow:

In response to Applicant's arguments that the specification provides a working example and clear guidance for determining the presence or absence of a hypertension-associated four-base pair insertion in the region specified by the claims, the Examiner respectfully disagrees. While it is noted that the specification and Examples therein provides a Table 2 at page 12 that shows an association analysis of NOS2A in hypertensive and normotensive subject, wherein a p-value of 0.016 is detected, it is unclear how the p-value relates to the four base pair insertion or how the data relates to determining a risk of hypertension in a subject. The data provides genotyping for subjects without the insertion - 313/313 (negative control), subjects with insertion - 313/317, and subjects without the insertion -317/317 (positive control).

When comparing the genotypes alleles in the hypertensive population studies versus the normotensive population, 55 out of 77 individual carried the 313/313 allele, whereas 64 out of 76

in the normotensive population carried the 313/317 allele. When comparing the genotypes alleles in the hypertensive population studies versus the normotensive population, 15 out of 77 individual carried the 313/317 allele, whereas 10 out of 76 in the normotensive population carried the 313/317 allele. When comparing the genotypes alleles in the hypertensive population studies versus the normotensive population, 7 out of 77 individual carried the 317/317 allele, whereas 2 out of 76 in the normotensive population carried the 317/317 allele. Thus, it is unclear from the results the significant difference between the hypertensive population versus the normotensive population. The results appears to be relatively similar in each population and thus the significant p-value indicated in the specification could merely be a comparison of sample comprising the insertion versus the controls in a single population. Additionally, it is unclear as to how one skilled in the art is to use the information to determine a risk of hypertension because the specification does not make clear what the four base pair sequence is or how it is deemed a risk polymorphism for hypertension. Currently, it appears from the specification and claims that any four base pair insertion within the region specified is considered a risk polymorphism regardless to whether or not the sequence is associated with hypertension or not.

In regards to Applicant's arguments that undue experimentation is not necessary because any four base pair insertion in the region specified can be identified by routine experimentation, it is noted the specification does not account for the lack of predictability in the art for one skilled in the art to extrapolate the results as claimed. There is a significant lack of predictability in the art for the instant invention as indicated by the teaching of Wacholder et al (see prior Office action). There is significant lack of predictability in the art for the instant invention

because one skilled in the art cannot readily anticipate the effects of any four base pair insertion (risk polymorphism) in any one population or sample size based on the numerous variabilities in the art and lack of direction, guidance and information provided in the specification. This is because it is not obvious from the disclosure or data given, what significant role the risk polymorphism(s), which encompasses any four base pair insertion within the specified region recited therein, play in determining a risk of hypertension or a risk of any other disease that may be associated therewith. Therefore, the Examiner maintains that undue experimentation is necessary to practice the invention as currently claimed.

In response to Applicant's lack of understanding for the statement "the claims can encompass any genotype, disease associated or not that can be found in the iNOS gene", it is noted that the statement was based on the claims as previously presented because the claims did not recite any method steps which limited detecting a specific risk polymorphism in the iNOS gene to the diagnosis of or predisposition of hypertension. While the currently amended claims recite a risk polymorphism in a specified region of the promoter of the iNOS gene, they do not clearly specify by sequence which of the plethora of risk polymorphisms that are encompassed by the claims as written are indicative of detecting a predisposition of or diagnosis of hypertension. Therefore, the currently amended claims not only encompass a four basepair insertion that may be associated with hypertension, but also encompasses additional four basepair mutation that my be silent or active and/or may be associated with hypentension or some other disease (not identified) besides hypertension.

In regards to Applicant's arguments concerning the Wacholder et al reference, it is noted that the reference clearly identifies the high level of unpredictability in the art concerning

mutation association studies as indicative of a diagnosis of a disease or condition in a population. As indicated earlier, it is unclear how the data recited therein is directly or indirectly conclusive of diagnosing a risk of hypertension or a predisposition to hypertension given the small differences in genotyping results between the hypertensive samples versus the normotensive samples (see Table 2).

Applicant's arguments are not sufficient to overcome the prior art rejection under 35 USC 112 first paragraph. Accordingly, the lack of enablement rejection is maintained.

Conclusion

8. No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
5/11/06